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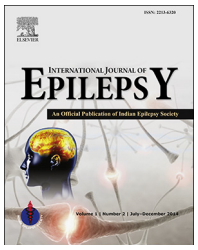

Original Article

Comparative assessment of Montreal Cognitive Assessment (MOCA) and Minimental State Examination (MMSE) in apolipoprotein E (APOE) ε4 allele carriers in epilepsy

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ABSTRACT

Background/Aim: Mini mental state examination (MMSE) is a widely accepted tool till date to investigate cognitive status; however, its sensitivity is questioned by few studies. Alternately, Montreal cognitive assessment (MOCA) is considered more effective with high sensitivity to assess cognitive status than MMSE. The usefulness of MOCA is well established in assessing cognitive status in patients in various disorders. Apolipoprotein E (APOE) ε4 allele is identified as one of the risk factors associated with cognitive impairment on MMSE; however, the usefulness of MOCA on the association between APOE ε4 allele and cognitive impairment is not clearly established and hence the present study.

Methods: This prospective study recruited 123 subjects diagnosed as tonic-clonic seizures in the study site during the study period.

Results: Gender and educational status showed normal cognitive function on MMSE but showed cognitive impairment on MOCA. Among epilepsy patients, all APOE ε4 carriers showed mild to severe cognitive impairment on MOCA but differences in cognitive status were observed in this population as well as in APOE ε4 non-carriers on MMSE.

Conclusion: Thus, the present study demonstrates the sensitivity of MOCA over MMSE in detecting cognitive impairment in epilepsy.

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1. Introduction

Dementia is a common adverse effect associated with phenytoin drug treatment in epilepsy population. It affects the quality of life of the individual besides taking treatment with AEDs and as such, its accurate diagnosis is of prime importance in epilepsy population. Currently dementia is assessed by using Mini Mental Status Examination (MMSE). MMSE is a brief mental status test measuring orientation, concentration, immediate and delayed memory, language, and constructional praxis.[1] Scores range from 0 to 30, with five cognitive subtests and higher scores indicating better cognitive performance. Until 2001, there were no specific cognitive screening instruments to detect mild dementia. Although the MMSE is considered useful, it has low sensitivity to detect mild dementia, because most subjects score in the normal range on the test.[2] So far, the assessment of cognitive function was solely based on the Mini-Mental State Examination (MMSE), which has been shown to be insensitive at detecting dementia.[3]

So, in cases in which there is suspicion of dementia or concern about the patient's cognitive status and the MMSE score is in the normal range (24–30), test such as the Montreal cognitive assessment (MOCA) could be administered. MOCA is a 30-point scale with seven cognitive subtests including visuospatial/executive functions, which are not found in MMSE. This would help to demonstrate objective cognitive loss.[4] MOCA is feasible and superior to the MMSE in screening for dementia in subacute stroke/transient ischemic attack patients, as it detects complex dementias such as executive function and visual perception/construction.[5] MOCA is more sensitive to changes in types of dementia that particularly affect the frontal lobe because of its greater emphasis on tasks of frontal executive functioning, compared with the MMSE, and therefore MOCA is a useful additional screening for individuals in a memory clinic setting, who score over 25 points on the MMSE.[6] In cryptogenic epilepsy patients, who reported normal cognition according to MMSE, MOCA performance showed dementia in these patients in spite of a normal MMSE score, thus suggests using MOCA as a screening test for patients with epilepsy.

Now there is increasing evidence that apolipoprotein E (APOE) genotyping will help to diagnose the Alzheimer's disease (AD), and several studies report that APOE ε4 allele carriers are vulnerable to the AD.[7] Studies also report that moderate to severe dementia results ultimately in AD, and moreover the possible role of APOE ε4 allele in dementia has been documented. Based on the above reports, in the present study, we compared MMSE and MOCA in assessing cognitive function in APOE ε4 allele carriers and in APOE ε4 allele non-carriers in epilepsy.

2. Methods

2.1. Study population

One hundred and twenty three epilepsy patients (≥18 years old) admitted to the Neurology Department at a private hospital in Erode, Tamilnadu, India were recruited during the period, November 2008 to September 2012. Ethical approval was granted by the Institutional Ethics Committee, Swamy Vivekanandha College of Pharmacy, Namakkal, Tamilnadu, India. The patient consent form was prepared in English and regional language (Tamil) as per the Indian Council of Medical Research (ICMR) guidelines, and the same was obtained before start of the study. All the epilepsy population (>18 years old) diagnosed as tonic-clonic seizures administered with phenytoin monotherapy were eligible participants, and patients were excluded, if they were illiterate, having active psychiatric illness and/or neurological disorders according to their medical history.

2.2. Procedure

2.2.1. Demographics and clinical profile

Basic demographic information including age, gender, and level of education were collected.

2.2.2. Mini Mental State Exam (MMSE)

Folstein's Mini Mental State Exam Form was used in this study.[1,8,9] It includes

Orientation: The object was asked the date, and then asked specifically for parts omitted.
Registration: The names of 3 unrelated objects, clearly and slowly were said, about 1 s for each. The most commonly used objects were apple, table, and penny. After said all 3, subject was asked to repeat them.
Attention and calculation: The subject was asked to begin with 100 and count backward by 7. Stop after 5 subtractions (93, 86, 79, 72, 65). The total number of correct answers was scored.
Recall: The subject was asked to recall the 3 words that they were previously asked to remember.
Language: It consists of Naming, Repetition, 3-stage command, Reading, Writing, and Copying.

2.2.3. Montreal Cognitive Assessment Scale

In addition to MMSE, MOCA scale was also used to assess different cognitive domains.[10–12] Time to administer the MOCA is approximately 10 min. The total possible score is 30 points. It also consists of

Alternating trail making: In this, subject was asked to draw a line going from a number to a letter in ascending order.
Visuoconstructional skills: The subject was asked to copy the diagram of cube and also draw a clock.
Naming: The subject was asked to name the animal given. One point each was given for each correct answer.
Memory: The examiner read a list of 5 words at a rate of one per second. The subject was asked to repeat the words later on.
Attention: It consists of forward digit span, backward digit span, and vigilance.
Sentence repetition: The examiner read out 2 sentences, and the subject was asked to repeat it.
Verbal fluency: The subject was asked to tell as many words as he can think of that begin with a particular alphabet.

Abstraction: The subject was asked to explain what each pair of words has in common.

2.2.4. *DNA extraction and APOE genotyping*

0.5 ml of venous blood sample was drawn from study population, and genomic DNA was extracted from blood sample using protocol given in DNA extraction kit (Genei labs, Bangalore, India). APOE was amplified by polymerase chain reaction (PCR) in a DNA thermocycler (Genei Labs, Bangalore, India) using following oligonucleotide primers obtained from Sigma Labs, India and following primer used in the PCR E2mut (5′-ACT GAC CCC GGT GGC GGA GGA GAC GCG TGC) and downstream primer E3 (5′-TGT TCC ACC AGG GGC CCC AGG CGC TCG CGG). After initial denaturation at 94 °C for 3 min, the samples were subjected to 40 cycles of denaturation at 94 °C for 30 s, annealing at 65 °C for 30 s and extension at 72 °C for 7 s. A final extension was performed at 72 °C for 7 s. Following PCR, aliquots (10 μl) of the reaction mixtures were analyzed by electrophoresis on a 1.5% agarose gel, containing ethidium bromide (0.2 mg/ml), in the presence of an appropriate DNA molecular weight marker. The amplification band was seen under UV transilluminater and detection of resistance gene with the use of marker. After PCR amplification restriction digests containing 10 μl amplified DNA, 2 μl of buffer and 1.5 U *Hae*II (Sigma Labs) were incubated at 37 °C overnight. The digested product was loaded onto a 12% nondenaturing polyacrylamide gel and electrophoresed for 2 h at constant voltage (60 V). The gel was stained with ethidium bromide (0.2 mg/L) for 10 min and visualized under UV illumination.[13]

2.2.5. *Statistical analysis*

To evaluate the effect of APOE ε4 allele on dementia, study population was categorized into two groups: ε4 carriers (ε2/ε4, ε4/ε4 and ε3/ε4 allele) and ε4 non-carriers (ε2/ε2, ε2/ε3 and ε3/ε3 allele). Differences between the mean ± SD of two groups (case and control) were analyzed by the two-tailed unpaired Student's *t*-test, and differences between median were analyzed by Mann–Whitney test. 95% confidence interval was used, and $P < 0.05$ was considered statistically significant. Graph pad In stat prism 4.0 software package was used in the statistical analysis.

3. Results

3.1. *Cognitive status in demographics of the study population*

Cognitive status between MMSE and MOCA was compared among the study population by using their demographics (Table 1). Irrespective of the gender distribution and age distribution, all the study population found to have mild to moderate dementia according to both MMSE and MOCA. However, Graduates found to have normal cognitive status according to MMSE and mild dementia according to MOCA. The difference was found to be significant ($P < 0.05$).

3.2. *Association of cognitive status and APOE ε4 allele*

An attempt was made to compare cognitive score using MMSE and MOCA in the total study population ($n = 123$) with the help of APOE allelic status. Among the study population 30.1% ($n = 37$) were detected as ε4 carriers and 69.9% ($n = 86$) were ε4 non-carriers (Table 2). APOE ε4 carriers were found to have moderate dementia on both MMSE and MOCA. A significant reduction ($P < 0.05$) in the cognitive status was observed on MOCA as compared to MMSE. Mean cognitive score of ε4 non-carriers was normal on MMSE, but mild dementia was observed in the same study population on MOCA.

3.3. *Comparison of MMSE and MOCA on cognitive status of ε4 carriers and ε4 non-carriers*

The prevalence rate of normal cognitive status, mild dementia, moderate dementia, and severe dementia among the ε4 carriers and ε4 non-carriers in both MMSE and MOCA was categorized according to their cognitive score (Table 3). MMSE showed no prevalence of severe dementia in both ε4 carriers and ε4 non-carriers. As per MOCA, 59.5% ($n = 22$) ε4 carriers and 19.8% ($n = 17$) ε4 non-carriers reported severe dementia (Alzheimer's disease) and no ε4 carriers showed normal cognitive status. Conversely, on MOCA, only 22.1% ($n = 19$) ε4 non-carriers showed normal cognitive score, while majority of ε4 non-carriers were found to have poor cognitive status.

Table 1 – Cognitive status in demographics of the study population ($n = 123$).

Variables	MMSE	MOCA	*P* value
Gender			
Male ($n = 93$)	24.09 ± 3.90	21.33 ± 4.02	**<0.05**
Female ($n = 30$)	24.65 ± 4.37	21.92 ± 4.58	**<0.05**
Age distribution			
Early adulthood (19–30 years; $n = 70$)	23.26 ± 4.17	20.70 ± 4.33	**<0.05**
Adulthood (31–50 years; $n = 53$)	23.92 ± 4.56	21.01 ± 4.68	**<0.05**
Educational status			
Primary (0–5th standard; $n = 28$)	22.27 ± 3.88	19.68 ± 4.15	**<0.05**
Secondary (6–12th standard; $n = 42$)	22.78 ± 4.57	19.70 ± 4.30	**<0.05**
Graduates (>12th standard; $n = 53$)	25.05 ± 4.17	22.71 ± 4.36	**<0.05**

Numbers indicate mean ± SD.
Significant *P* values (<0.05) are in bold face.

Table 2 – Association of cognitive status with APOE ε4 allele.

Total study population (n = 123)	MMSE (mean ± SD)	MOCA (mean ± SD)	P value
ε4 carriers (n = 37)	19.89 ± 3.79	17.56 ± 3.92	**<0.05**
ε4 non-carriers (n = 86)	25.25 ± 3.58	22.47 ± 3.92	**<0.05**

Significant P values (<0.05) are in bold face.

Table 3 – Cognitive status of ε4 carriers and ε4 non-carriers using MMSE and MOCA (n = 123).

Variables	ε4 carriers (n = 37)		ε4 non-carriers (n = 86)		P value[a]
	Number (%)	Score (mean ± SD)	Number (%)	Score (mean ± SD)	
MMSE score (0–30)					
Normal (>24)	5 (13.5)	25.40 ± 0.54	53 (61.6)	27.67 ± 1.86	**<0.05**
Mild cognitive impairment (21–24)	9 (24.3)	23.55 ± 0.52	22 (25.6)	22.45 ± 0.96	**<0.05**
Moderate cognitive impairment (10–20)	23 (62.2)	17.26 ± 1.93	11 (12.8)	19.18 ± 0.60	**<0.05**
Severe cognitive impairment (<10)	–	–	–	–	–
MOCA score (0–30)					
Normal (>25)	–	–	19 (22.1)	28.33 ± 1.10	–
Mild cognitive impairment (19–25)	15 (40.5)	21.66 ± 1.34	50 (58.1)	22.18 ± 2.08	**<0.05**
Severe cognitive impairment [Alzheimer's disease (<19)]	22 (59.5)	14.77 ± 2.24	17 (19.8)	17.17 ± 0.88	**<0.05**

[a] ε4 carriers score vs. ε4 non-carriers score.
Significant P values (<0.05) are in bold face.

4. Discussion

The present study clearly demonstrates the sensitivity of MOCA over MMSE toward the detection of dementia in epilepsy patients. Previous studies report vulnerability of APOE ε4 toward dementia and AD[4,7] and the same is highlighted in this study. Significant variation ($P < 0.05$) in cognitive score was observed between MMSE and MOCA in the epilepsy population in the present study.

Similarity was observed between MMSE and MOCA scores on cognitive status among the gender and age distribution of the study population. However, a significant difference ($P < 0.05$) was observed in educational status between MMSE and MOCA among the graduates. Our findings are consistent with earlier reports that the prevalence of dementia and associated patient correlated factors might occur in a range of domains of the MOCA.[6] The usefulness of MOCA over MMSE in the assessment of cognitive status is also established in Parkinsonism,[14] stroke,[5] and epilepsy.[6]

One important finding in the present study is that dementia was detectable with MOCA rather than MMSE among the APOE ε4 non-carriers. The poor performance of the MMSE at detecting dementia in this population may be due to several factors. The MMSE is less capable of testing for complex dementia in domains such as visuospatial, executive function, and abstract reasoning. In addition, the MMSE subtests of Attention and Delayed Recall contain test items, which are not as challenging as contained in the MOCA.[5]

APOE is encoded by a gene on chromosome 19[126] and can be translated by 3 major alleles ε2, ε3 and ε4.[15,16] The most common allele present in the general population is the ε3 variant and the rarest is ε2, although racial and ethnic differences have been related to the distribution of the alleles.[17–20] APOE ε4 allele in developing AD and/or affecting normal cognition.[21] Apolipoprotein E ε4 carriers have a tendency toward more severe dementia[22] and are also vulnerable to earlier onset and more rapidly progressing AD.[23] Therefore early detection of dementia by MOCA screening may help clinicians to intervene and improve prognosis in epilepsy.

According to MOCA, no subject among ε4 carriers reported normal cognitive score, whereas mild to severe dementia (AD) was observed in the same population. On the contrary, 13.5% ε4 carriers showed normal cognitive status, and no ε4 carrier was found with severe dementia. The results from the present study indicate that both ε4 carriers and ε4 non-carriers were found to have significantly greater decline in cognitive score by MOCA screening, and moreover cognitive status in ε4 carriers was poorer than that in ε4 non-carriers on MOCA rather than MMSE. Our finding substantiates the results of the previous study about the sensitivity of the MOCA over MMSE.[5,6] The findings of the present study propose that detection of dementia in epilepsy population particularly in APOE ε4 non-carriers by the currently used MMSE screening is questionable and therefore recommends MOCA as a more reliable tool for the assessment of cognitive score in epilepsy.

Conflicts of interest

All authors have none to declare.

REFERENCES

1. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189–198.

2. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004;256:183–194.
3. Perneczky R, Wagenpfeil S, Komossa K, Grimmer T, Diehl J, Kurz A. Mapping scores onto stages: mini-mental state examination and clinical dementia rating. *Am J Geriatr Psychiatry*. 2006;14:139–144.
4. Howard C, Ziad N, Yves J, et al. Mild cognitive impairment and cognitive impairment, no dementia: part A, concept and diagnosis. *Alzheimer's Dement*. 2007;3:266–282.
5. YanHong D, Vijay KS, Bernard PC, et al. The Montreal Cognitive Assessment (MoCA) is superior to the Mini-Mental State Examination (MMSE) for the detection of vascular cognitive impairment after acute stroke. *J Neurol Sci*. 2010;299:15–18.
6. Tasha S, Nadia G, Clive H. The Montreal Cognitive Assessment: validity and utility in a memory clinic setting. *Can J Psychiatry*. 2007;52:329–332.
7. Ranjan D, Warren B, David L, Lisa B. The basis for disease-modifying treatments for Alzheimer's disease: the Sixth Annual Mild Cognitive Impairment Symposium. *Alzheimer's Dement*. 2009;5:66–74.
8. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the mini-mental state examination by age and educational level. *JAMA*. 1993;269:2386–2391.
9. Phabphal K, Kanjanasatien J. Montreal Cognitive Assessment in cryptogenic epilepsy patients with normal Mini-Mental State Examination scores. *Epileptic Disord*. 2011;13:375–381.
10. Adrian W, Pauline K, Anne C, et al. The validity, reliability and utility of the Cantonese Montreal Cognitive Assessment (MoCA) in Chinese patients with confluent white matter lesions. *Hong Kong Med J*. 2008;14:7.
11. Nasreddine ZS, Phillips NA, B_dirian V. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53:695–699.
12. Martin I, Youngah S, Michael CI, et al. Genotyping of apolipoprotein E: comparative evaluation of different protocols. *Curr Protoc Hum Genet*. 2003;38:. 9.14.1–9.14.13.
13. Ihl R, Frölich TD, Martin EM. Differential validity of psychometric tests in dementia of Alzheimer type. *Psychiatr Res*. 1992;44:93–106.
14. Nazem S, Siderowf AD, Duda JE, et al. Montreal cognitive assessment performance in patients with Parkinson's disease with "normal" global cognition according to mini-mental state examination score. *J Am Geriatr Soc*. 2009;57:304–308.
15. Zannis VI, Breslow JL. Human very low density lipoprotein apolipoprotein E isoprotein polymorphism is explained by genetic variation and posttranslational modification. *Biochemistry*. 1981;20:1033–1041.
16. Zannis VI, Just PW, Breslow JL. Human apolipoprotein E isoprotein subclasses are genetically determined. *Am J Hum Genet*. 1981;33:11–24.
17. Crews DE, Kamboh MI, Mancilha-Carvalho JJ, Kottke B. Population genetics of apolipoprotein A-4, E, and H polymorphisms in Yanomami Indians of northwestern Brazil: associations with lipids, lipoproteins, and carbohydrate metabolism. *Hum Biol*. 1993;65:211–224.
18. Demarchi DA, Salzano FM, Altuna ME, et al. APOE polymorphism distribution among Native Americans and related populations. *Ann Hum Biol*. 2005;32:351–365.
19. Gerdes LU, Gerdes C, Hansen PS, Klausen IC, Faergeman O, Dyerberg J. The apolipoprotein E polymorphism in Greenland Inuit in its global perspective. *Hum Genet*. 1996;98:546–550.
20. Nagy B, Karadi I, Fintor L, Rigo J, Romics L, Papp Z. Apolipoprotein E genepolymorphism frequencies in a sample of healthy Hungarians. *Clin Chim Acta*. 1999;282:147–150.
21. Henderson AS, Easteal S, Jorm AF, et al. Apolipoprotein E allele epsilon 4, dementia, and cognitive decline in a population sample. *Lancet*. 1995;346:1387–1390.
22. Carsten E, Karl H, Elke K, Wolf-Dieter H. Cortical acetylcholine esterase activity and ApoE4-allele in Alzheimer disease. *Neurosci Lett*. 2006;408:46–50.
23. Martins CA, Oulhaj A, De Jager CA, Williams JH. APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model. *Neurology*. 2005;65:1888–1893.